## APPLICANTS' INTERVIEW SUMMARY RECORD

Applicants and Applicants' representatives thank Supervisory Patent Examiner Anthony Caputa and Examiner Christopher Yaen for the courtesy of the telephonic interview of June 18, 2003 in connection with the above-identified application.

Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicants present this interview Summary Record of the telephonic interview of June 18, 2003 ("the Interview") between Supervisory Patent Examiner Anthony Caputa and Examiner Christopher Yaen, Dr. H. Perry Fell on behalf of the licensee of the above-identified application, and Applicants' representatives, Adriane M. Antler and Muna Abu-Shaar, in connection with the above-referenced application. During the Interview, the outstanding Office Action was discussed, as detailed below.

### A. The Rejections Under 35 U.S.C. § 112, Second Paragraph

With respect to the rejection of claims 101-118 for lack of definiteness due to the recitation of the terms "antibody" and "agent," Supervisory Patent Examiner Caputa and Examiner Yaen indicated the rejections would be withdrawn in view of Applicants' arguments regarding the commonly known definition of the term "antibody" and the definition in the specification of the term "agent."

### B. The Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiners indicated that the rejection of claims 101-118 under 35 U.S.C. § 112, first paragraph, for lack of enablement of immunoconjugates other than those comprising the antigen-binding regions of BR96, would be withdrawn in view of Applicants' argument that the present specification meets the threshold of enablement established for the production of antibodies by *In re Wands*.

### C. The Obviousness-Type Double-Patenting Rejection

Dr. Antler requested that the obviousness-type double-patenting rejection be held in abeyance until the claims are indicated to be allowable but for the double-patenting rejection, at which point Applicants intend to submit a terminal disclaimer. The Examiners agreed.

**D. The Rejections Under 35 U.S.C. § 102**

Dr. Antler noted that the allegedly anticipatory references cited by the Examiner, *i.e.*, Zara and Yeh, are not prior art to the present invention because the present claims are entitled to their priority date of June 30, 1989.

Examiner Yaen indicated that he would review the priority cases to ensure that the present claims are entitled to the June 30, 1989 priority date, and would withdraw the rejections under 35 U.S.C. § 102 if he found the claims to be entitled to the priority date.

**E. The Rejections Under 35 U.S.C. § 103**

Applicants' representatives discussed with Supervisory Patent Examiner Caputa and Examiner Christopher Yaen why the presently claimed invention is not rendered obvious by Abe, alone or in combination with Oldham. In particular, Dr. Antler provided two lines of reasoning as to why Abe does not suggest the instant invention. First, evidence indicates that the antibody taught in Abe, AH6, binds to a different Lewis Y epitope than BR96, and thus would not be expected to competitively inhibit the binding of BR96 to a carcinoma cell. Further, Abe, at best, suggests the use of AH6 for *in vitro* diagnostics, but does not provide any suggestion or teaching that AH6 can be internalized into cells or would have therapeutic utility as an immunoconjugate. Accordingly, Abe does not teach or suggest the antibody portion of the immunoconjugate of claim 101, let alone the immunoconjugate itself.

The Examiners indicated that Applicants' arguments would be considered when submitted in writing in response to the outstanding Office Action.

Further details of Applicants' arguments presented at the Interview are provided below.

## REMARKS

Claims 59-65, 71, 86, and 93-118 are pending in the instant application. Claims 59-65, 71, 86, and 93-100 have been cancelled as drawn to a non-elected invention. Claim 107 has been canceled without prejudice. Applicants reserve the right to pursue the subject matter of this claim in one or more related applications. Claims 108, 117 and 118 have been rewritten as claims 122, 123 and 124, respectively, to incorporate dependencies on new claims and remove dependencies upon canceled claims. New claims 119-121 and 125-128, drawn to specific embodiments of the present invention, have been added. No new matter has been added.

Support for new claim 119 can be found in the specification at page 56, lines 25-30. Support for new claim 120 can be found in the specification at page 89, lines 12-17. Support for new claim 121 can be found in the specification at page 15, line 34. Support for new claims 125 and 127 can be found in the specification, for example at page 30, lines 17-35. Support for new claims 126 and 128 can be found in the specification, for example at page 73, lines 24-30. Following entry of the amendments made herein, claims 101-105 and 109-128 will be pending in the instant application.

## I. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 101-118 are rejected under 35 U.S.C. § 112, second paragraph, allegedly as indefinite for failing to particularly point out and distinctly claim that which Applicants regard as the invention. According to the Examiner, the specification does not make clear the meaning of the terms "antibody" and "agent," rendering the claims indefinite.

Applicants note that claim 107 has been canceled without prejudice and thus the rejection as applied to claim 107 is moot. Further, claims 108, 117 and 118 have been rewritten as claims 122, 123 and 124, respectively. With respect to the rejection of claims 101-106, 108 (rewritten as claim 122) and 109-116, 117 (rewritten as claim 123) and 118 (rewritten as claim 124), Applicants respectfully disagree with the Examiner and submit that one of skill in the art at the time the present application was filed could easily discern the meanings of "antibody" and "agent," as discussed below.

With respect to the recitation of the term "antibody," Applicants submit that the term "antibody" is a term commonly known in the art that does not require a specific definition in the specification. For example, in a reference prior to the effective filing date of the present application, Baruj Benacerraf and Emil R. Unanue, Textbook of Immunology 283 (1979) (attached as Exhibit A) define antibody as "an immunoglobulin molecule capable of combining specifically with a known substance (antigen)." Applicants submit that the meaning of the term "antibody" was well known to one of skill in the art at the time the present application was effectively filed, as evidenced by King and Spalding, and thus the rejection is in error and should be withdrawn.

With respect to the recitation of the term "agent," Applicants direct the Examiner's attention to page 28, lines 1-3 of the specification, which defines a therapeutic agent as one that is "useful for therapy including anti-tumor drugs, cytotoxins, cytotoxin agents, and radioactive agents." The specification at page 28, lines 13-14 further defines a cytotoxin as an agent "that is detrimental to cells." With respect to the Examiner's query as to whether Diphtheria toxin is intended to be encompassed by the term "therapeutic agent," Applicants note that one of skill in the art would recognize that, because Diphtheria toxin is detrimental to cells, it would be considered a cytotoxin or cytotoxin agent, and thus a therapeutic agent as that term is used by the present claims.

In view of the foregoing remarks, Applicants submit that the rejections under 35 U.S.C. § 112, second paragraph have been obviated and should be withdrawn.

## II. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 101-118 are rejected under 35 U.S.C. § 112, first paragraph, allegedly as lacking enablement for immunoconjugates other than those containing the antigen binding regions of BR96. Applicants note that claim 107 has been canceled without prejudice and thus the rejection as applied to claim 107 is moot. Further, claims 108, 117 and 118 have been rewritten as claims 122, 123 and 124, respectively. With respect to the rejection of claims 101-106, 108 (rewritten as claim 122), 109-116, 117 (rewritten as claim 123) and 118 (rewritten as claim 124), Applicants respectfully disagree, for the reasons discussed below.

## A. The Legal Standard for Enablement

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); *see also DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover,* 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis

to conclude that the amount of experimentation is undue in *In re Angstadt,* 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.
>
> *Id.* at 219 (emphasis in the original).

Further, in the application of the law of enablement to antibody-related inventions, the Examiner's attention is directed to *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), in which the Federal Circuit reversed a Patent Office rejection of claims directed to immunoassays of hepatitis B surface antigen using high affinity monoclonal IgM antibodies for lack of enablement. The court concluded that, even without a hybridoma deposit, undue experimentation would not be required to practice the invention. In arriving at its decision, the court noted that the finding of enablement was "consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980." *Wands*, 858 F.2d at 736, citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94.

In the instant application, effectively filed in 1989, *i.e.*, 9 years after the filing of the *Wands* application, not only was the methodology available for obtaining and screening antibodies known in the art, but the specification provides ample teachings on how antibodies comprising variable regions other than those of BR96 could be obtained and screened. For example, the specification at pages 31-33 describes the process of generating antibodies using purified Lewis Y, cell extracts containing Lewis Y, or the breast cancer cell line 3396 as immunogens. The specification at pages 98-101 (Example 1) and page 107, Table 2 enumerates other types of cells that express the BR96 antigen and that can potentially be useful as immunogens for generating antibodies that competitively inhibit the binding of BR96 to a carcinoma cell. The present specification further notes (at page 37, lines 33-35) that the antibodies of the invention can be made that differ in species origin relative to BR96. Thus, one of skill in the art can, using any

of the immunogens described in the specification, immunize a rat, rabbit, chicken, guinea pig, or even a mouse of a different strain than that used for the generation of BR96 (*i.e.*, a strain other than BALB/c (see page 98, line 14)). Immunization of any of these species or strains that differs from BALB/c should result in the generation of antibodies whose heavy chains differ in sequence from BR96, and yet are characterized with similar epitope specificity to BR96 and thus competitively inhibit the binding of BR96 to a carcinoma cell.

The present application further demonstrates that utilizing the methods disclosed in the application allowed the recovery of the BR96 antibody, and thus one of skill in the art would expect that repeating the procedure would result in the identification of other antibodies that competitively inhibit the binding of BR96 to a carcinoma cell. Additionally, methods for determining whether one antibody competitively inhibits the binding of another antibody to its target are known in the art, and an example is described in the specification at page 140, lines 19-28, and at pages 154-155.

Thus, the generation and screening of antibodies of the invention is made routine by the use of methods that were well known to the skilled artisan at the effective filing date of the present application, and by the deposit of the hybridoma secreting the BR96 antibody with the American Type Culture Collection.

Post filing-date evidence also supports Applicants' position that antibodies that competitively inhibit the binding of BR96 to carcinoma cells and that comprise variable regions other than the BR96 variable region can be made. In particular, Applicants draw the Examiner's attention to U.S. Patent No. 5,728,821 to Yelton *et al.* ("Yelton"), a copy of which is attached hereto as Exhibit B. Yelton describes experiments in which a codon mutagenesis of the BR96 complementarity determining regions was performed. Not only was Yelton able to identify variants of BR96 that bound to Lewis Y and tumor cells, but several variants were identified that had an increased affinity to Lewis Y relative to a chimeric antibody comprising the native BR96 variable region (*see, e.g.*, Yelton at columns 7 and 8, including Table 1), and such mutant antibodies would be expected by one of skill in the art to competitively inhibit the binding of BR96 to a carcinoma cell. Further, because antibodies comprising complementarity determining region sequences that differ from those of BR96 and yet retain the specificity of BR96 have been identified

and can be made, one of skill in the art would conclude that other antibodies with the same binding specificity as BR96 can be made. The Examiner has not provided any evidence to the contrary.

Applicants take this opportunity to remind the Examiner that it is the Examiner's burden to explain his conclusory statements regarding the lack of enablement of claims of the scope presently being claimed. In particular, the Examiner is reminded of MPEP § 2164.04, which states that:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 U.S.P.Q. at 370. (emphasis added)

Applicants submit that, given the routine nature of making and screening antibodies (as the Federal Circuit noted in *In re Wands*), the teachings of the specification, the deposit of the BR96 antibody, and the Examiner's failure to cite a

reasoned basis for his allegations of non-enablement, the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement is in error and must be withdrawn.

## III. THE REJECTION UNDER OBVIOUSNESS-TYPE DOUBLE PATENTING SHOULD BE WITHDRAWN

Claims 101-109 and 112-118 have been rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 23-29 and 32-33 of U.S. Patent No. 5,980,896. Applicants note that claim 107 has been canceled without prejudice and thus the rejection as applied to claim 107 is moot. Further, claim 108 has been rewritten as claim 122.

With respect to claims 101-106, 108 (*i.e.*, new claim 122), 109 and 112-118, Applicants respectfully request that the double-patenting rejection be held in abeyance until the present claims are indicated to be allowable but for the double-patenting rejection, at which time Applicants intend to submit a Terminal Disclaimer, thereby obviating the rejection.

## IV. THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 101, 102, 104, 105, 107, 108, 117 and 118 are rejected under 35 U.S.C. § 102(b), allegedly as anticipated by Zara *et al.* (1991, Anal. Biochem. 194(1):156-62)("Zara"). Claims 101, 103, 108-109, and 116-118 are rejected under 35 U.S.C. § 102(b), allegedly as anticipated by Yeh *et al.* (1992, Int. J. Cancer 51(2):274-82)("Yeh").

Applicants note that claim 107 has been canceled without prejudice and thus the rejection as applied to claim 107 is moot. Further, claims 108, 117 and 118 have been rewritten as claims 122, 123 and 124, respectively.

Without admitting that Zara or Yeh discloses the presently claimed invention, Applicants submit that neither Zara nor Yeh is prior art to the presently claimed invention. Applicants submit that the presently claimed invention was effectively filed on June 30, 1989, prior to the publication date of both Zara and Yeh.

The present application is a continuation of U.S. Patent Application No. 08/077,253, which was filed on June 3, 1993 and issued as U.S. Patent No. 5,980,896 on

November 11, 1999 ("the 253 application"). The '253 application is a continuation-in-part of U.S. Patent Application No. 08/057,444, which was filed on May 5, 1993 and issued as U.S. Patent No. 5,491,088 on February 13, 1996 ("the 444 application"); The '444 application is a continuation of U.S. Patent Application No. 07/544,246, which was filed on June 26, 1990, now abandoned ("the 246 application") and the '246 application is a continuation-in-part of U.S. Patent Application No. 07/374,947 ("the 0947 application"), which was filed on June 30, 1989, also abandoned. This priority claim is evidenced by the filing receipt for this application, a copy of which is attached hereto as Exhibit C.

To be entitled to the benefit under 35 U.S.C. § 120 of the filing date of an earlier filed United States application, the earlier filed application must (a) meet the requirements of 35 U.S.C. § 112, first paragraph, with respect to the claims of the United States application claiming the benefit of priority thereto; (b) be copending with the subsequently filed application claiming the benefit of priority thereto; (c) be referenced in the subsequently filed application claiming the benefit of priority thereto and (d) name at least one inventor in common named in the subsequently filed application claiming the benefit of priority thereto.

Applicants submit that, for the reasons discussed below, each of the foregoing requirements for priority under 35 U.S.C. § 120 have been met, and thus the present claims are fully entitled to the benefit of the June 30, 1989 filing date of the '947 application.

**A. The Requirements of 35 U.S.C. § 112, First Paragraph**

The requirements of Section 112, first paragraph, are the "enablement," "written description" and "best mode" requirements.

1. Enablement

With respect to the enablement requirement, Applicants have discussed extensively why the presently claimed invention is fully enabled. Applicant's basis for their argument that the presently claimed invention is fully enabled (routine nature of making and screening antibodies, the teachings of the specification, and the deposit of the BR96 hybridoma) is equally applicable to the June 30, 1989 filing date of the '947

application. This enabling disclosure is maintained throughout the priority chain of applications, and thus the enablement requirement of § 120 has been met.

2. Written Description

The specification of the '947 application order reasonably conveys to the artisan that Applicants had possession of the subject matter presently claimed.

Specifically, Applicants note to the Examiner that support for the claims that will be pending following entry of the amendments made herein and rejected as anticipated by Zara and/or Yeh (*i.e.*, claims 101-105, 108, 109, and 116-118) can be found in the '947 application, as follows:

| **Claim** | **Claim Language** | **Support in U.S. Patent Application Nos. 07/374,947.** |
|---|---|---|
| *101* | An immunoconjugate | Page 8, lines 16-17. |
| | that comprises an antibody joined to a therapeutic agent, | Page 19, lines 20-22. |
| | wherein the antibody comprises an immunoglobulin or antigen-binding fragment thereof | Page 14, lines 30-31 |
| | that competitively inhibits binding of the monoclonal antibody BR96 [to a carcinoma cell] | Page 15, lines 4-7; claim 7 as filed. [Page 11, lines 8-10] |
| | as produced by the hybridoma deposited with the ATCC and assigned Accession No. HB10036. | Page 13, lines 26-31. |
| *102* | The immunoconjugate of claim 101, the antibody is a monoclonal antibody or a fragment of a monoclonal antibody | Page 12, lines 1-2; claim 3 as filed. |
| *103* | The immunoconjugate of claim 101, wherein the antibody is a Fab, $F(ab')_2$ or Fv fragment | Page 12, lines 1-2; claim 3 as filed |
| *104* | The immunoconjugate of claim 101, wherein the antibody is a bifunctional antibody with a binding specificity for two different antigens. | Page 21, lines 15-19; claim 19 as filed. |
| *105* | The immunoconjugate of claim 101, wherein | Page 15, lines 22-26. |

| | | |
|---|---|---|
| | the antibody is a chimeric antibody. | |
| *108*[1] | The immunoconjugate of claim 101, 102, 105, 106, or 107, which is purified | Page 26, line 27-30. |
| *109* | The immunoconjugate of claim 101 wherein the therapeutic agent is selected from the group consisting of a cytotoxin, an anti-tumor drug, a radioactive agent, a second antibody, and an enzyme | Page 19, lines 20-24; page 20, lines 9-10 and 16-19. |
| *116* | The immunoconjugate of claim 109 which is purified | Page 26, line 27-30 |
| *117*[2] | A pharmaceutical composition, comprising a pharmaceutically effective amount of the immunoconjugate of claim 101, 102, 105, 106, or 107, and a pharmaceutically acceptable carrier. | Page 21, line 28 though page 22, line 3 and page 22, line 22-23. |
| *118*[3] | The pharmaceutical composition of claim 117, wherein the immunoconjugate is purified. | Page 26, line 27-30 |

The relevant text providing written description support is maintained throughout the priority chain of applications.

3. Best Mode

The best mode requirement is believed satisfied for each of the priority applications as well as the present application.

**B. Co-Pendency of Priority Applications**

Under § 120, a subsequently filed application will be entitled to the benefit of the filing date of an earlier filed application as long as the two applications were co-pending. There is no limit to the number of prior applications through which a chain of codependency may be traced.

Applicants note that the present application claims § 120 benefit to a chain of co-pending applications, all the way back to the '947 application: the present invention, filed on April 13, 1999 was co-pending with the '253 application, which issued into a patent on

[1] This claim has been renumbered as claim 122.
[2] This claim has been renumbered as claim 123.

November 9, 1999; the '253 application, filed on June 14, 1993 was co-pending with the '444 application, which issued into a patent on February 13, 1996; the '444 application, filed on May 5, 1993, was co-pending with the '246 application, which was abandoned on May 29, 1993; the '246 application, filed on June 26, 1990, was co-pending with the '947 application, which was filed on June 30, 1989 and abandoned on December 10, 1991.

**C. Cross Referencing Requirements**

For a subsequently filed application to be accorded the benefit of the filing date of an earlier filed application under § 120, the subsequently filed application must contain or be amended to contain a reference to the prior application or applications.

Each of the applications in the chain of the present application cross-references the prior application(s) in the chain. Accordingly, the cross-referencing requirement for § 120 benefit has been met.

**D. Inventor in Common**

In order to claim the benefit of the filing date of an earlier filed application, the prior application must name as an inventor at least one inventor named in the later filed application. 37 C.F.R. § 1.78(a). All the applications in the priority chain of the present application name Ingegerg Hellstrom and Karl Erik Hellstrom as inventors. Accordingly, the requirement that each pair of co-pending applications name as an inventor at least one common inventor has been satisfied.

**E. Conclusion Regarding Priority**

In view of the foregoing remarks, Applicants submit that the present claims are entitled to the benefit of the June 30, 1989 filing date of U.S. Patent Application No. 07/374,947, and accordingly Zara and Yeh are not prior art to the present claims.

In view of the foregoing remarks, Applicants submit that the rejections under 35 U.S.C. § 102(b) are in error and should be withdrawn.

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[3] This claim has been renumbered as claim 124.

## V. THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 101-118 are rejected under 35 U.S.C. § 103(a), allegedly as being obvious over Abe *et al.*, 1986, *Cancer Res.* 46:2639-44 ("Abe") in view of the teachings of Oldham *et al.*, 1983, *J. Biol. Resp. Modif.* 2:1-37 ("Oldham"). In particular, according to the Examiner, Abe teaches the antibody AH6 that is able to react with the Lewis Y ("$Le^Y$") antigen on a colon carcinoma cell, and Oldham teaches that antibodies can be coupled to therapeutic agents and that such conjugates are useful in the treatment of cancer. The Examiner concludes that the teaching of the Abe and Oldham, when combined, provide the suggestion and the motivation to grant one of ordinary skill in the art the reasonable expectation of success in arriving at the claimed invention. In response, Applicants respectfully disagree, and submit that the Examiner has not established a *prima facie* case of obviousness.

Applicants first note that claim 107 has been canceled without prejudice. Thus, the rejection of this claim is moot. Claims 108, 117 and 118 have been rewritten as claims 122, 123 and 124, respectively.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate that the combined references teach or suggest all claim limitations, and provide a reasonable expectation of success in arriving at the claimed invention. In addition, the Examiner must establish that there exists, either within the references themselves or in the general knowledge of the art, some motivation or suggestion to combine or modify the teaching of the prior art to produce the claimed invention. *See, e.g., In re Mayne*, 104 F.3d 1339, 1341-42, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997). The combination of Abe and Oldham fails in each of these respects, as discussed below.

### A. The Cited References Do Not Teach All Limitations

The presently claimed invention is directed to an immunoconjugate comprising an antibody that competitively inhibits the binding of the monoclonal antibody BR96 to a carcinoma cell. It is expected, however, that AH6, the antibody disclosed in Abe, would likely not compete with BR96 for binding to Lewis Y because AH6 and BR96 recognize different epitopes. According to the instant specification, BR96 recognizes both the $Le^X$

and $Le^y$ determinants (page 116, lines 25-27; FIGS. 11 and 12). Moreover, BR96 is highly specific for carcinomas (and a small number of specific normal tissues; *see* pages 104-105); thus, it is expected to preferentially bind to the extended form of $Le^y$. *See* Kim *et al.*, "Expression of $Le^y$ and Extended $Le^y$ Blood Group-related Antigens in Human Malignant, Premalignant, and Nonmalignant Colonic Tissues," *Cancer Res.* 46:5985-92 (1986) ("Kim"[4]; abstract) (extended form of $Le^y$ is associated with malignancy and premalignancy). Antibody AH6, however, recognizes $Le^y$, but does not recognize extended $Le^y$ (*id.*, at Table 1). It is predicted, therefore, that BR96 and AH6 recognize different epitopes. As a result, AH6 is not expected to competitively inhibit the binding of BR96 to a carcinoma cell.

Because antibody AH6, disclosed by Abe, is not expected to compete with BR96 for binding to a carcinoma cell, Abe fails to teach this critical limitation of the claims. Oldham fails to remedy this deficiency, as it contains no disclosure regarding AH6, or any other Lewis Y-binding antibodies. Thus, the combination of Abe and Oldham cannot render any of the pending or new claims obvious.

**B. <u>There is No Motivation to Combine the Cited References</u>**

The presently claimed invention is directed to an immunoconjugate comprising (1) an antibody that competitively inhibits the binding of the monoclonal antibody BR96 to a carcinoma cell; and (2) a therapeutic agent. Because there is no suggestion of the therapeutic utility of such antibodies within Abe, there is no motivation to combine Abe with Oldham to make conjugates to a therapeutic agent.

Firstly, Abe discloses AH6, an Lewis Y antibody, and studies its expression. Abe concludes that AH6 has *diagnostic* utility for colon cancer, and may have *prognostic* value for identifying the degree of malignant potential in polyps. Abe does not suggest a therapeutic use for AH6. Moreover, the experiments in Abe are all performed *in vitro*; thus, Abe presents no teaching or suggestion of usefulness *in vivo*. Also, the diagnostic agents conjugated were not, to Applicants' knowledge, suggested in the art for *in vivo* therapeutics. For example, neither the cited references nor the art taught that a

[4] Cited by Applicants in the Information Disclosure Statement filed August 9, 2000 as reference HC.

radioactive agent, such as that recited in claim 109, could be used in an immunoconjugate for *in vitro* therapy.

Furthermore, because the immunoconjugates of the invention comprise antibodies that competitively inhibit the binding of BR96 to a carcinoma cell, these immunoconjugates are predicted to be internalized within their target cells, as are BR96 and BR96-containing conjugates. As a result, the claimed immunoconjugates are expected to have therapeutic utility.

The requirement for immunoconjugate internalization into a target cell was known in the art at the time of the filing of the instant application. For example, Schlom, in MOLECULAR FOUNDATIONS OF ONCOLOGY, Broder, Ed., Williams and Wilkins, pp. 95-134 (1991) ("Schlom"), cited in a previous Office Action, observes that the fact "that some solid tumor membrane antigens are stable cell surface components suggests that a subset of mAb drug conjugates will be ineffective against these target antigens" (p. 107) and that the "necessity of the mAb conjugate to internalize for cytotoxic activity" provides a "theoretical limitation to the potential usefulness of mAb drug or toxin conjugates as effective oncolytic agents" (p. 107). Schlom's position regarding antibody-drug conjugates is substantiated by the art generally. For example, the Examiner's attention is directed to the Amendment submitted on May 6, 2002 in connection with the above-identified application, which discusses numerous examples of antibodies that are not internalized, rendering them of little to no utility as drug delivery reagents.

Abe, conversely, does not teach or suggest that AH6, a Lewis Y antibody, is internalized into its target cell, and would thus useful for drug delivery purposes. Instead, Abe only concludes that AH6 has utility for the *diagnosis* of colon cancer, and for the *prognosis* of colon polyps. Oldham also fails to teach or suggest that AH6 is internalized. Thus, there is no suggestion or motivation within the cited references themselves to combine them to arrive at the claimed invention. Likewise, this suggestion or motivation is absent from the art, which teaches generally that *internalized* tumor-binding antibodies, but not tumor-binding antibodies generally, may be used to create therapeutic immunoconjugates. In fact, because the internalization of antibodies within cells is unpredictable in nature, one of skill in the art would not be motivated to make

immunoconjugates that competitively inhibit the binding of BR96 to carcinoma cells without benefit of the teachings of Applicant's disclosure.

Given the lack of motivation, one of skill in the art would additionally not have combined the references to arrive at the claimed invention, wherein the recited immunoconjugate is a drug, as recited in claim 121. In view of the foregoing, Applicants respectfully request the Examiner withdraw the rejection of the claims under 35 U.S.C. § 103(a).

## INFORMATION DISCLOSURE STATEMENT

The Zara and Yeh references cited by the Examiner were only provided to Applicants as PubMed abstracts. Accordingly, Applicants submit herewith a Supplemental Information Disclosure Statement to make the full-length Zara and Yeh references of record in the instant application.

## CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application. Claims 101-106, 109-116 and 119-128 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections and allowance and action for issuance are respectfully requested.

Applicant respectfully requests that the Examiner call the undersigned attorney at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date August 4, 2003

Adriane M. Antler 32,605
Adriane M. Antler (Reg. No.)

By: Muna Abu-Shaar
Muna Abu-Shaar
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**PENNIE & EDMONDS LLP**
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures